II. REMARKS

Claims 71 to 79 and 85 to 109 are pending. New claim 110 has been added herein. Thus, when the claim amendments made herein are entered, claims 71 to 79 and 85 to 110 will be pending.

A. Regarding the amendments

Claims 71 and 72 have been amended herein by more clearly indicating that the subject ribozyme (claim 71) or nucleic acid molecule (claim 72) is administered locally. The amendment is supported in the specification, for example, at page 17, line 27 to page 18, line 8, which makes clear that the compositions of the invention can be administered locally.

Claim 85 has been amended to more clearly indicate that the ribozyme of claim 71 is administered intraocularly. The amendment is supported in the specification, for example, at page 18, line 6-8, and by claim 85 as originally filed. Claim 86 has been amended to solely depend on claim 71. The amendment is supported in the specification, for example, by claim 86 as originally filed.

Claim 106 has been amended so as to recite only SEQ ID NO: 4145, and to more clearly indicate that the RNA encoding the cyclin PCNA includes this sequence. The

amendment is supported in the specification, for example, by Table 3, at page 20.

Claim 107 has been amended to more clearly indicate SEQ ID NOS: 4381, 4382, 4383, 4384 and 4385. The amendment is supported in the specification, for example, by Table 17 (page 26) and Example 3 (pages 28-29). Claim 108 has been amended to recite SEQ ID NO: 4385, instead of SEQ ID NO: 4383. The amendment is supported in the specification, for example, at page 28, line 25.

New claim 110 is directed to the nucleic acid molecule of claim 72 being administered intraocularly. The new claim is supported in the specification, for example, at page 18, line 6-8, and by claim 85 as originally filed.

Because the amendments made herein are fully supported by the specification, no issue of new matter arises.

B. Regarding the indefiniteness rejections

1. Claims 85 and 86.

Claims 85 and 86 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, it is alleged that there is no antecedent basis for the term "nucleic acid molecule" in claim 71. Applicants respectfully traverse the rejection.

In response, claim 85 has been amended herein by deleting the term "nucleic acid molecule" and to solely depend on claim 71. Similarly, claim 86 has been amended herein to solely depend on claim 71. In addition, new claim 110, which recites the term "nucleic acid molecule," solely depends on claim 72.

In view of these amendments, Applicants respectfully request that this rejection be withdrawn.

2. Claims 107 and 108.

Claims 107 and 108 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, it is alleged that it is unclear what the members of the group are due to the recited term "and." Applicants respectfully traverse the rejection.

Claim 107 has been amended herein by deleting this term "and," and by more clearly indicating that the recited group consists of SEQ ID NOS: 4381, 4382, 4383, 4384 and 4385. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. Regarding the enablement rejection

Claims 71 to 78 and 85 to 108 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Applicants respectfully traverse the

rejection, taking each issue addressed in the Action separately.

1. PVR

The Office Action alleges that the specification enables a method of treating proliferative vitreoretinopathy (PVR), but does not enable treating generally any proliferative eye disease.

In response, enclosed herewith is a declaration from Joan Robbins, the first named inventor of the subject application. Exhibit A of the declaration shows that a ribozyme of the subject invention is effective in treating another proliferative eye disease, specifically, trabeculectomy, which is the post-operative closure of a surgical drainage site made in the eye. Typically, a trabeculectomy is done to relieve intra-ocular pressure due to glaucoma. See declaration, para. 3.

More specifically, a ribozyme of the invention, SEQ ID NO: 4385, maintained the drainage site open for at least 14 days in most rabbits. Declaration, para. 4. Thirty days after the trabeculectomy, histological examination of the site revealed thinning of the sclera and a partially opened drainage site in a large number of treated rabbits. Thus, the data show that a ribozyme of the invention was effective in treating trabeculectomy. Declaration, para. 4.

Furthermore, the specification already provides data showing that a ribozyme of the invention is effective in treating another proliferative disease, namely, scar prevention due to surgical incision. See Example 9 of the specification, pages 45-47. Specifically, the specification discloses that, 36 days after wounding, histopathological examination revealed that ribozyme treated wounds were more completely healed and less scarred than untreated wounds.

In summary, the data provided in the subject application and in the attached declaration show that a ribozyme of the invention is effective in treating or preventing three distinct conditions: a) PVR; b) trabeculectomy; and c) scar formation. The only factor that links these three conditions is that they are proliferative diseases involving a cyclin PCNA. See declaration, para. 6. Accordingly, the specification enables administering a ribozyme of the invention to treat any proliferative disease involving a cyclin PCNA, and certainly any such proliferative eye disease, as is claimed.

As a side point, the Action alleges that the recited term "proliferative eye disease" would include scarring of the eyelid and melanoma of the eyelid. In response, Applicants respectfully submit that the eyelid is skin. Therefore, while (as discussed above) scarring of the skin has indeed be enabled through experimental data disclosed in the specification, such diseases of the eyelid

are not encompassed by the term "proliferative eye disease."

2. Systemic delivery.

The Office Action concedes that the specification provides examples where a ribozyme of the invention is effective when administered locally. However, the Action alleges that the specification does not provide guidance for systemic delivery.

In response, claims 71 and 72 (and all claims dependent thereon) have been amended herein to more clearly indicate that the compositions of the invention are administered locally.

3. Vectors.

The Office Action also rejects the claims, in part, because it alleges that the specification does not enable delivery of a ribozyme by any means other than intravitreal injection. More specifically, the Action alleges that the specification does not provide guidance with respect to delivery by means of a vector.

In response, attached to the enclosed declaration is Exhibit B. The exhibit shows the results of human vascular smooth muscle cells being transduced with an adeno-associated virus (AAV) vector adapted to express a PCNA ribozyme of the invention. As shown by Exhibit B, the

vector expressing the PCNA ribozyme was very effective in inhibiting cellular proliferation. See Declaration, para. 8. Thus, the data supports enablement of the specification of means of delivering a ribozyme of the invention locally, either with or without use of a vector.

4. SEQ ID NO: 4383.

The Office Action alleges that, in view of the results shown in Table 23 of the specification (page 45), SEQ ID NO: 4385 provided significant improvement of PVR, but use of SEQ ID NO: 4383 did not appear to provide the same treatment effect.

In response, Applicants respectfully submit that, in order to be enabling, SEQ ID NO: 4383 does not need to be as effective as SEQ ID NO: 4385 in treating PVR. Rather, SEQ ID NO: 4383 merely needs to be shown to be effective. And, indeed, as provided by Table 23 of the specification, SEQ ID NO: 4383 is shown to be effective, as compared to the control.

Therefore, the results shown in Table 23 prove to the contrary: that **both** ribozymes tested were effective in treating PVR. The common denominator of these ribozymes is that they were designed to cleave PCNA. In view of these results, it would not have not required undue experimentation for the skilled artisan to use any ribozyme that cleaves PCNA in treating PVR, or any other proliferative eye disease.

Moreover, both ribozymes of the invention, SEQ ID NO: 4385 and SEQ ID NO: 4383, were designed to cleave the specific PCNA target of SEQ ID NO: 4145. In fact, both ribozymes were effective *in vivo* in such cleavage and, therefore, in treating proliferative eye disease. In view of these results, the skilled artisan would certainly have considered the specification enabling, at the very least, for treating a proliferative eye disease with a ribozyme that cleaves RNA encoding a cyclin PCNA, wherein such RNA comprises SEQ ID NO: 4145, as is now recited by claim 106.

5. Antisense technology.

The Office Action also bases its rejection, in part, on the notion that ribozyme technology is unpredictable. In support of this contention, the Action analogizes ribozyme technology with antisense technology and, therefore, provides several references directed mainly to antisense technology.

In response, Applicants respectfully submit that it is not correct to include ribozymes in the same category with antisense molecules and to classify ribozyme therapy as an "unpredictable art" similar to antisense therapy. Antisense molecules consist of any series of contiguous bases generally ranging in size from 15 to 25 nucleotides. The number of possible 20mer antisense molecules that could be directed at a typical mRNA target of, for example, three kilobases is about 150, just considering simple linear coverage without taking into account all possible

permutations (e.g. n-1, n-2, n-3 …n-19). With this in mind, it is not at all surprising that the Branch reference (TIBS 1998) cited by the Office Action reports that it was necessary to screen 34 antisense molecules to c-raf to find an effective one, with 40% showing no activity.

In contrast, the rules for selecting ribozyme sites are much more defined. "The state of the art with regard to designing hairpin ribozymes is such that we can design with a reasonably high level of confidence a ribozyme that will cleave an oligonucleotide target using the rules described above." Yu and Burke 1997, attached to this Response as Exhibit 1. " A large number of heterologous targets have been successfully cleaved using these targeting rules. The methods described allow logical development of an optimally active hairpin ribozyme." Hampel et al 1997, attached to this Response as Exhibit 2. Since ribozymes cleave mRNA molecules at specific recognition sites, a small and finite set of possible therapeutic ribozymes can be identified. Yu and Burke suggest selecting 3-6 target sites to find one with "optimal" cleavage.

In further support of the idea that ribozyme technology is far more predictable than antisense, attached to the enclosed declaration is Exhibit C. This exhibit provides data showing the activity of 6 ribozymes which were designed according to the applicable rules for hairpin ribozymes to target six of the 12 possible ribozyme cleavage sites for IL-1 beta mRNA. <u>All six</u> ribozymes reduced mRNA

levels greater than 50% and 5 out of 6 reduced protein levels greater than 50%. See declaration, para. 9.

Moreover, as discussed above, the ribozymes of the invention have been effective *in vivo*. Specifically, ribozymes of the invention were tested and found effective in treating animals with a) PVR; b) scars; and c)trabeculectomy. In view of the predictability of ribozyme design and the effective results of *in vivo* experiments with using such ribozymes of the invention, the skilled artisan would have considered the subject specification enabling for the claimed methods without undue experimentation.

III. CONCLUSION

In light of the Remarks herein, Applicants respectfully submit that the claims are now in condition for allowance and requests a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

Respectfully submitted,

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Amended version:

71. (Amended) A method of treating a proliferative eye disease, comprising administering locally to a patient a therapeutically effective amount of a ribozyme which cleaves RNA encoding a cyclin PCNA, such that said proliferative eye disease is treated.

72. (Amended) A method of treating a proliferative eye disease, comprising administering locally to a patient an effective amount of a nucleic acid molecule comprising a promoter operably linked to a nucleic acid segment encoding a ribozyme which cleaves RNA encoding a cyclin PCNA, such that said proliferative eye disease is treated.

85. (Amended) The method according to claim 71 ~~claims 71 or 72~~ wherein said ribozyme ~~or nucleic acid molecule~~ is administered intraocularly.

86. (Amended) The method according to claim 71 ~~or 72~~ wherein said ribozyme is formulated within a solution.

106. (Amended) The method according to claims 71 or 72 wherein said RNA encoding said cyclin PCNA ~~PCNA cyclin~~ comprises SEQ ID NO: 4145. ~~a sequence selected from the group consisting of SEQ ID NOS: 3855 to 4115 and 4143 to 4152~~

107. (Amended) The method according to claims 71 or 72 wherein said ribozyme comprises a sequence selected from

the group consisting of SEQ ID NOS: 4381, 4382, 4383, 4384 and 4385 ~~and 4381 to 4385~~.

108. (Amended) The method of claim 107, wherein said sequence is SEQ ID NO: 4385 ~~4383~~.